UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,324	01/04/2002	H. William Bosch	029318-0107	2223

31049 7590 09/28/2010

Elan Drug Delivery, Inc. c/o Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, DC 20007-5109

EXAMINER	
HAGHIGHATIAN, MINA	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
09/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WILLIAM H. BOSCH, DONNA M. MARCERA,
KEVIN D. OSTRANDER, NIELS P. RYDE and DOUGLAS A. WHITE

Appeal 2010-005029
Application 10/035,324
Technology Center 1600

Before RICHARD E. SCHAFER, MICHAEL P. TIERNEY, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

LEBOVITZ, *Administrative Patent Judge.*

DECISION ON APPEAL[1]

---

[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

This is a decision on the appeal under 35 U.S.C. § 134 by the Patent Applicant from the Patent Examiner's rejections of claims 1-7, 9-11, 13, 14, and 35-37. The Board's jurisdiction for this appeal is under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to a sterile nanoparticulate dispersion comprising tyloxapol and beclomethasone or budesonide particles. The dispersion is recited to be free from biological contaminants. Tyloxapol is a surface stabilizer which is "adsorbed onto the surface of the nanoparticulate beclomethasone and/or nanoparticulate budesonide particles." (Claim 1). The dispersion can be used as an oral inhalant to treat asthma (Spec. 7-9). According to the Specification, the "present invention is directed to the unexpected discovery that nanoparticulate compositions of beclomethasone or budesonide having tyloxapol as a surface stabilizer can be readily sterilized by sterile filtration." (*Id.* at 9).

Claims 1-7, 9-11, 13, 14, and 35-37 stand rejected by the Examiner under 35 U.S.C. § 103(a) as obvious in view of:

1) Wiedmann,[2] Desai,[3] and Verrecchia[4] (Ans. 4); and

2) Wood, [5] Desai, and Verrecchia (*id.* at 7).

Because Appellants relied on the same arguments for both rejections (App. Br. 19), we consider the rejections together.

---

[2] U.S. Patent 5,747,001 issued May 5, 1998.
[3] U.S. Patent Application Publication 2007/0117862 A1 published May 24, 2007.
[4] U.S. Patent 6,139,870 issued Oct. 31, 2000.
[5] WO 96/25918 published Aug. 29, 1996.

Claim 1 is representative and reads as follows:

1. A sterile, stable nanoparticulate dispersion comprising:

(a) a liquid dispersion medium;

(b) nanoparticulate beclomethasone particles, nanoparticulate budesonide particles or a combination thereof dispersed in the dispersion medium, the nanoparticulate beclomethasone and nanoparticulate budesonide particles having an effective average particle size of less than 150 nm;

(c) tyloxapol as a surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles in an amount effective to prevent the aggregation of the nanoparticulate beclomethasone and/or budesonide particles; and

(d) optionally, at least one secondary surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles,

wherein the nanoparticulate dispersion is free from biological contaminants by sterile filtration with a filter having a pore size of 0.2 μm or less.

ISSUES

Whether it would have been obvious to persons of ordinary skill in the art to have sterile-filtered the Wiedmann and Wood preparations as taught by Desai and Verrecchia.

Whether Appellants provided sufficient evidence to rebut the Examiner's obviousness determination.

LEGAL PRINCIPLES

"An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

"One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward – that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

"For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Unexpected results must also be "commensurate in scope with the degree of protection sought by the claimed subject matter." *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

FACTUAL FINDINGS ("FF")

Desai

1. Desai describes particles for delivery of pharmacologically active agents. (Desai, ¶ [0001].)

2. Desai discloses that its nanoparticle formulations can be sterile-filtered.

> The invention further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter), which can be sterile-filtered through a 0.22 micron filter. This is achieved by addition of a water soluble solvent (e.g. ethanol) to the organic phase and by carefully selecting the type of organic phase, the phase fraction and the drug concentration in the organic phase. The ability to form nanoparticles of a size that is filterable by 0.22 micron filters is of great importance and significance, since formulations which contain a significant amount of any protein (e.g., albumin), cannot be sterilized by conventional methods such as autoclaving, due to the heat coagulation of the protein.

(Desai, ¶ [0051].)

3. The method described by Desai involves combining an organic solvent having a dissolved active agent, water or an aqueous solution surfactant, and cosurfactant to form an emulsion, and then removing the organic solvent to produce a suspension of nanoparticles of the active agent (*id.* at ¶¶ [0094] – [0100]).

4. In a further embodiment, Desai teaches that the drug particles are coated with protein (*id.* at ¶¶ [0101] – [0104]).

5. Desai discloses that its compositions can be prepared without conventional surfactants, but instead employing protein as a stabilizing agent (Desai, ¶¶ [0047] & [0050]).

6. In describing its process of making nanoparticles with a protein employed as stabilizing agent, Desai states that "[u]nlike conventional methods for nanoparticle formation, no surfactant . . . is added to the mixture." (*Id.* at ¶ [0163].)

7. Beclomethasone and budesonide are among a list of exemplary pharmacologically active agents (*id.* at ¶¶ [0115] & [0112] – [0156]).

8. Desai describes various solvents (*id.* at ¶¶ [0161] & [0169]) and proteins (*id.* at ¶ [0175]) that can be employed in its methods.

9. Desai also describes different surfactants and cosurfactants that can be employed to form spontaneous microemulsions (*id.* at ¶¶ [0271], [0272], & [0274] – [0280]).

10. In the nanoparticles that comprise surfactants and cosurfactants, Desai states that matrix-forming polymers (such as PVP) may be added to the solvent and the "stabilization and solid-form properties may be altered by the addition of water soluble polymer other than the protein (CMC, gums, and the like)" (*id.* at ¶¶ [0283] – [0284]).

Verrecchia

11. Verrecchia describes a method of making particles of less than 100 nm which can be filtered through a 0.22 µm filter.

> It has now been found, and this forms the subject of the present invention, that particles can be prepared, 95% of which have an average diameter of less than 100 nm . . . which can thus be subjected to a sterile filtration on 0.22 µm filters without a loss in yield. These particles are moreover more stable than those which could be obtained according to the prior art and can be lyophilized without leading to any phenomenon of particle agglomeration.
>
> According to the invention, the nanoparticles comprise at least one hydrophobic, water-insoluble and water-indispersible polymer or copolymer emulsified in a solution or aqueous dispersion of phospholipids and of an oleic acid salt, in particular sodium oleate.
>
> According to the invention, an active principle may be introduced with the polymer or the copolymer into the nanoparticles.

(Verrecchia, col. 1, ll. 25-43.)

Wiedmann

12. Wiedmann describes tyloxapol as a polymer and preferred surface stabilizer for beclomethasone nanoparticles (Wiedmann, col. 4, ll. 52-67; col. 2, ll. 20-37).

Answer

13. We adopt the factual findings of the Examiner on pages 3-9 of the Answer with respect to the Wiedmann, Woods, Desai, and Verrecchia publications.

ANALYSIS

Claim 1 is directed to a "sterile, stable nanoparticulate dispersion" comprising "(b) nanoparticulate beclomethasone particles" or "nanoparticulate budesonide particles" having an average particle size of less than 150 nm and "(c) tyloxapol as a surface stabilizer." The "nanoparticulate dispersion is free from biological contaminants by sterile filtration with a filter having a pore size of 0.2 μm or less."

The Examiner found that Wiedmann and Wood described the claimed dispersion with nanoparticulate particles coated with tyloxapol as a surface stabilizer, but did not disclose that the dispersion "is free from biological contaminants by sterile filtration with a filter having a pore size of 0.2 μm or less," as recited in claim 1. (Ans. 4 & 7-8.) However, the Examiner found that each of Desai and Verrecchia taught that filtration of nanoparticle dispersions through filters was conventional and determined it obvious to have applied these teachings to Wiedmann or Wood "because sterilized formulations are safer and beneficial to recipients" (*Id.* at 7 & 9).

Appellants do not challenge the Examiner's findings regarding the Wiedmann and Wood publications nor the difference between Wiedmann and Wood and the subject matter of claim 1. Rather, Appellants contend:

> the primary disagreement between Appellants and the Examiner is whether sterile filtration of a nanoparticulate dispersion is a known technique (as evidenced by Desai and Verrecchia) and/or whether Appellants provided sufficient evidence of unpredictability in the art of sterile filtration of nanoparticles to rebut the Examiner's broad interpretation of the cited references.

(App. Br. 10.)

Sterile Filtration

Appellants contend that the Examiner did not establish, based on Desai and Verrecchia, that it would have been obvious to apply sterile filtration to the Wiedmann and Wood dispersions. (App. Br. 10-11.)

With regard to Desai, Appellants contend that the "type of dispersion which can be sterilized by filtration as taught by Desai is limited to an albumin-bound isoreserpine particle dispersion. This is the only type of dispersion taught in the examples of Desai that is shown to be capable of sterile filtration." (App. Br. 12.) Appellants argue that the Examiner has improperly expanded Desai's teachings beyond what is enabled. (*Id.*)

Appellants' narrow reading of Desai is not supported by the evidence. In paragraph [0051], Desai describes methods to produce particles of a size which can be sterile-filtered through a 0.22 micron filter (FF2). There is no evidence that this disclosed method was intended to be restricted to the specific working examples. To the contrary, the broad disclosure in Desai of different types of active agents, solvents, and formulations (FF3 & FF7-10) would have led the skilled worker to reasonably expect that Desai's method

could be successfully employed to produce nanoparticles of a suitable size for sterile filtration, including those based on protein or those with surfactants and cosurfactants. The instant claims do not exclude dispersions comprising protein and/or surfactants.

In sum, Appellants have not provided a persuasive reason as to why the skilled worker would have restricted Desai's teachings to its working examples, when Desai expressly characterized its invention broadly as providing "for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter), which can be sterile-filtered through a 0.22 micron filter" (FF2).

Appellants also disputed whether tyloxapol would have been recognized as a component which could be substituted in Desai's nanoparticle formulations (App. Br. 12-13). Appellants' argument appears much the same as that above, i.e., that it would not have been reasonably predicted that formulations other than those explicitly described in Desai could be sterile-filtered.

Desai expressly described nanoparticle formulations comprising surfactants and cosurfactants (FF3 & FF9). In describing this embodiment, Desai stated that the nanoparticles can include other components, including *polymers* "other than proteins" to alter the stabilization properties (FF10). Thus, Desai did not exclude the addition of other components to its nanoparticle formulations. Since tyloxapol is described by Wiedmann as a polymer that can serve as a stabilizer (FF12), Desai's polymer disclosure (FF10) reasonably suggests tyloxapol's addition to the nanoparticle formulation. As sterile filtration was Desai's stated objective (FF2), persons of ordinary skill in the art would also have reasonably expected that the

addition of tyloxapol to Desai's formulations would not have impeded the latter's ability to be sterile-filtered.

Appellants also contend that Desai "teaches away" from the claimed invention because it stated that its formulation is prepared in the absence of conventional surfactants (Reply Br. 8). While it is correct that Desai makes such a statement (FF5), Desai also describes alternative embodiments in which surfactants are employed (FF9 & FF10).

Appellants contend that Verrecchia does not support the Examiner's position because it "does not teach a nanoparticulate dispersion having solid particles in a dispersion medium." (App. Br. 10.)

The dispersion of claim 1 comprises "nanoparticulate . . . particles." Appellants have not identified claim language or specification disclosure that would distinguish this particle type from the particles disclosed in Verrecchia.

Unpredictable Results

Appellants contend that it was not predictable that any combination of active agent and stabilizer in the form of a nanoparticulate dispersion could be sterile-filtered (App. Br. 10). To support this position, they rely on 18 examples disclosed in the Specification on pages 20-29.

To show obviousness, it must be established that the ordinary skilled worker in the art recognized "a reasonable expectation of success in making the invention in light of the prior art." *Amgen*, 580 F.3d at 1362. In this case, Appellants cited evidence from the Specification that was said to show when surface stabilizers other than tyloxapol were utilized to make

nanoparticulates, they did not produce preparations that could be sterile-filtered (App. Br. 15).

Claim 1 is a product claim which is not restricted to a particular process of preparing sterile nanoparticles. Both Desai and Verrecchia describe methods of making nanoparticles capable of sterile filtration (FF2 & FF11). Thus, persons of ordinary skill in the art would have known of methods for producing particles of a sterile filterable size. Based on these teachings, persons of ordinary skill in the art would therefore have reasonably expected that nanoparticles filterable through a sterile filter, such as the beclomethasone/tyloxapol nanoparticles suggested by Wiedmann (F12), could have been made by following the methods described in Desai or Verrecchia.

Unexpected Results

In addition to arguing that there was a lack of predictability, Appellants also contend that the claimed invention is based on the following unexpected findings:

> (i) that nanoparticulate active agents stabilized by surface stabilizers other than tyloxapol were unable to be sterile filtered; and (ii) that steroids other than budesonide and beclomethasone stabilized by tyloxapol were unable to be sterile filtered.

(Reply Br. 8.)

Examples 1-14 described on pages 20-27 of the Specification involve the use of tyloxapol and other surface stabilizers to prepare nanoparticulate compositions.

There must be a nexus between the evidence of unexpected results and the merits of the claimed invention. *See In re GPAC*, 57 F.3d at 1580.

Thus, it must be shown that the unexpected results arise from a limitation or feature of the claimed invention. In this case, the claims are drawn to a combination of tyloxapol with beclomethasone or budesonide. Appellants contend that it was unexpected that tyloxapol would produce sterile-filterable particles, while other surface stabilizers would not. "[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." *Ex parte Ishizaka*, 24 U.S.P.Q.2d 1621, 1624 (Bd. Pat. App. & Inter. 1992). Thus, it was Appellants' burden to show that tyloxapol, but not other surface stabilizers, would produce particles of the claimed size – and that it was tyloxapol, but not other factors or conditions, responsible for this result.

On pages 15-16 of the Appeal Brief, Appellants summarized Examples 1-18 described in the Specification, stating the "inventors of the present invention unexpectedly discovered that nanoparticulate active agents stabilized by surface stabilizers other than tyloxapol and having a particle size of less than 200 nm were unable to be sterile filtered (*see* Examples 5-9 and 12-14)." The only examples Appellants specifically referred to were Examples 5 and 8, which use HPMC and polysorbate 80, respectively, instead of tyloxapol. Appellants did not state whether the examples with HPMC and polysorbate 80 were performed under the same process conditions as the example dispersions prepared with tyloxapol – using the same ratio of active agent, surface stabilizer, and water solvent. Thus, Appellant has not met their burden of showing that it was the tyloxapol responsible for the result, rather than the process conditions or some other factor.

It was also not established that the tyloxapol alone was responsible for the result, or, for instance, whether it was the specific concentration of tyloxapol, the ratio between tyloxapol and the drug, or the water, that accounted for the result. Claim 1 is not restricted to a specific concentration of tyloxapol, a ratio between tyloxapol and the drug, or water as the dispersive medium.

Consequently, we conclude that Appellants have not established a nexus between the claimed subject matter and the results, nor that the results are commensurate with the scope of the claims. *Harris*, 409 F.3d at 1344. Appellants also did not state that such results would have been unexpected or surprisingly to a person of ordinary skill in the art." *In re Soni*, 54 F.3d at 750.

Examples 15-18, described on pages 27-29 of the Specification, involve the use of tyloxapol with active agents other than beclomethasone and budesonide. Again, Appellants did not establish that these examples were performed under the same conditions as the comparative examples with beclomethasone and budesonide. For the same reasons stated above, we do not consider these results sufficient to rebut the Examiner's case.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

bim

ELAN DRUG DELIVERY
C/O FOLEY & LARDNER, LLP
3000 K STREET, N.W.
SUITE 500
WASHINGTON, DC 20007-5109